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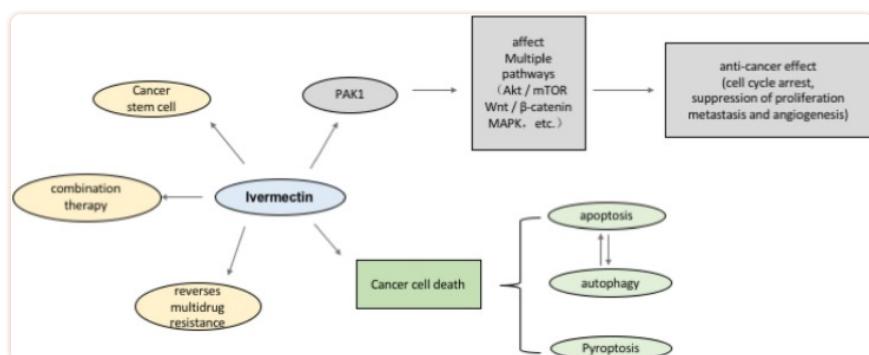
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Ivermectin, a potential anticancer drug derived from an antiparasitic drug

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Graphical abstract

Ivermectin has powerful antitumor effects, including the inhibition of proliferation, metastasis, and angiogenic activity, in a variety of cancer cells. This may be related to the regulation of multiple signaling pathways by ivermectin through PAK1 kinase. On the other hand, ivermectin promotes programmed cancer cell death, including apoptosis, autophagy and pyroptosis. Ivermectin induces apoptosis and autophagy is mutually regulated. Interestingly, ivermectin can also inhibit tumor stem cells and reverse multidrug resistance and exerts the optimal effect when used in combination with other chemotherapy drugs.



Abbreviations: ASC, Apoptosis-associated speck-like protein containing a CARD; ALCAR, acetyl-L-carnitine; CSCs, Cancer stem cells; DAMP, Damage-associated molecular pattern; EGFR, Epidermal growth factor receptor; EBV, Epstein-Barr virus; EMT, Epithelial mesenchymal-transition; GABA, Gamma-aminobutyric acid; GSDMD, Gasdermin D; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HER2, Human epidermal growth factor receptor 2; HMGB1, High mobility group box-1 protein; HSP27, Heat shock protein 27; LD50, median lethal dose; LDH, Lactate dehydrogenase; IVM, Ivermectin; MDR, Multidrug resistance; NAC, N-acetyl-L-cysteine; OCT-4, Octamer-binding protein 4; PAK1, P-21-activated kinases 1; PAMP, Pathogen-associated molecular pattern; PARP, poly (ADP- ribose) polymerase; P-gp, P-glycoprotein; PRR, pattern recognition receptor; ROS, Reactive oxygen species; STAT3, Signal transducer and activator of

transcription 3; SID, SIN3-interaction domain; siRNA, small interfering RNA; SOX-2, SRY-box 2; TNBC, Triple-negative breast cancer; YAP1, Yes-associated protein 1

Chemical compounds reviewed in this article: ivermectin(PubChem CID: 6321424), avermectin(PubChem CID: 6434889), selamectin(PubChem CID: 9578507), doramectin(PubChem CID: 9832750), moxidectin(PubChem CID: 9832912)

Keywords: ivermectin, cancer, drug repositioning

Abstract

Ivermectin is a macrolide antiparasitic drug with a 16-membered ring that is widely used for the treatment of many parasitic diseases such as river blindness, elephantiasis and scabies. Satoshi ōmura and William C. Campbell won the 2015 Nobel Prize in Physiology or Medicine for the discovery of the excellent efficacy of ivermectin against parasitic diseases. Recently, ivermectin has been reported to inhibit the proliferation of several tumor cells by regulating multiple signaling pathways. This suggests that ivermectin may be an anticancer drug with great potential. Here, we reviewed the related mechanisms by which ivermectin inhibited the development of different cancers and promoted programmed cell death and discussed the prospects for the clinical application of ivermectin as an anticancer drug for neoplasm therapy.

1. Introduction

Ivermectin(IVM) is a macrolide antiparasitic drug with a 16-membered ring derived from avermectin that is composed of 80% 22,23-dihydroavermectin-B1a and 20% 22,23-dihydroavermectin-B1b [1]. In addition to IVM, the current avermectin family members include selamectin, doramectin and moxidectin [2], [3], [4], [5] (Fig. 1). IVM is currently the most successful avermectin family drug and was approved by the FDA for use in humans in 1978 [6]. It has a good effect on the treatment of parasitic diseases such as river blindness, elephantiasis, and scabies. The discoverers of IVM, Japanese scientist Satoshi ōmura and Irish scientist William C. Campbell, won the Nobel Prize in Physiology or Medicine in 2015 [7,8]. IVM activates glutamate-gated chloride channels in the parasite, causing a large amount of chloride ion influx and neuronal hyperpolarization, thereby leading to the release of gamma-aminobutyric acid (GABA) to destroy nerves, and the nerve transmission of muscle cells induces the paralysis of somatic muscles to kill parasites [9,10]. IVM has also shown beneficial effects against other parasitic diseases, such as malaria [11,12], trypanosomiasis [13], schistosomiasis [14], trichinosis [15] and leishmaniasis [16].

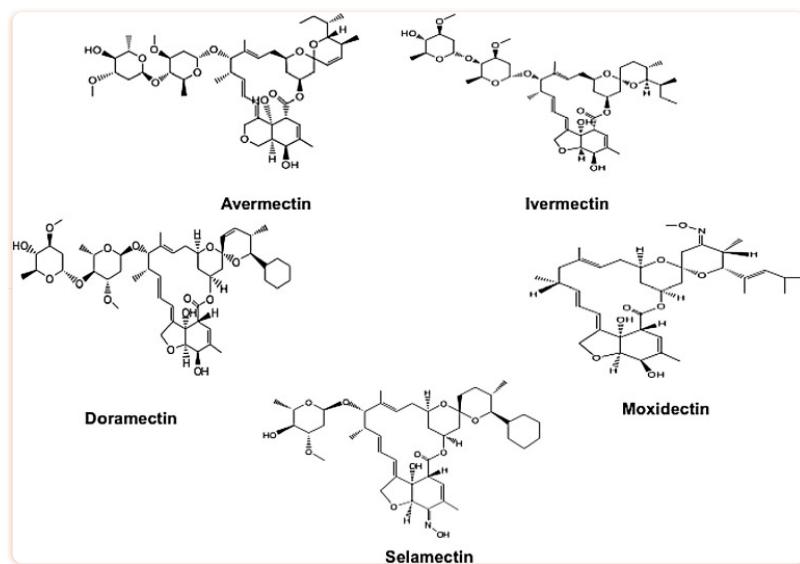


Fig. 1

The chemical structures of ivermectin and other avermectin family compounds in this review.

IVM not only has strong effects on parasites but also has potential antiviral effects. IVM can inhibit the replication of flavivirus by targeting the NS3 helicase [17]; it also blocks the nuclear transport of viral proteins by acting on α/β -mediated nuclear transport and exerts antiviral activity against the HIV-1 and dengue viruses [18]. Recent studies have also pointed out that it has a promising inhibitory effect on the SARS-CoV-2 virus, which has caused a global outbreak in 2020 [19]. In addition, IVM shows potential for clinical application in asthma [20] and neurological diseases [21]. Recently scientists have discovered that IVM has a strong anticancer effect.

Since the first report that IVM could reverse tumor multidrug resistance (MDR) in 1996 [22], a few relevant studies have emphasized the potential use of IVM as a new cancer

treatment [[23], [24], [25], [26], [27]]. Despite the large number of related studies, there are still some key issues that have not been resolved. First of all, the specific mechanism of IVM-mediated cytotoxicity in tumor cells is unclear; it may be related to the effect of IVM on various signaling pathways, but it is not very clear overall. Second, IVM seems to induce mixed cell death in tumor cells, which is also a controversial issue. Therefore, this review summarized the latest findings on the anticancer effect of IVM and discussed the mechanism of the inhibition of tumor proliferation and the way that IVM induces tumor programmed cell death to provide a theoretical basis for the use of IVM as a potential anticancer drug. As the cost of the research and development of new anticancer drugs continues to increase, drug repositioning has become increasingly important. Drug repositioning refers to the development of new drug indications that have been approved for clinical use [28]. For some older drugs that are widely used for their original indications and have clinical data and safety information, drug repositioning allows them to be developed via a cheaper and faster cycle and to be used more effectively in clinical use clinically

[29]. Here, we systematically summarized the anticancer effect and mechanism of IVM, which is of great significance for the repositioning of IVM for cancer treatment.

2. The role of IVM in different cancers

2.1. Breast cancer

Breast cancer is a malignant tumor produced by gene mutation in breast epithelial cells caused by multiple carcinogens. The incidence of breast cancer has increased each year, and it has become one of the female malignant tumors with the highest incidence in globally. On average, a new case is diagnosed every 18 seconds worldwide [30,31]. After treatment with IVM, the proliferation of multiple breast cancer cell lines including MCF-7, MDA-MB-231 and MCF-10 was significantly reduced. The mechanism involved the inhibition by IVM of the Akt/mTOR pathway to induce autophagy and p-21-activated kinase 1(PAK1)was the target of IVM for breast cancer [32]. Furthermore, Diao's study showed that IVM could inhibit the proliferation of the canine breast tumor cell lines CMT7364 and CIPp by blocking the cell cycle without increasing apoptosis, and the mechanism of IVM may be related to the inhibition of the Wnt pathway [33].

Triple-negative breast cancer (TNBC) refers to cancer that is negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2(HER2) and is the most aggressive subtype of breast cancer with the worst prognosis. In addition, there is also no clinically applicable therapeutic drug currently [34,35]. A drug screening study of TNBC showed that IVM could be used as a SIN3-interaction domain (SID) mimic to selectively block the interaction between SID and paired a-helix2. In addition, IVM regulated the expression of the epithelial mesenchymal-transition (EMT) related gene E-cadherin to restore the sensitivity of TNBC cells to tamoxifen, which implies the possibility that IVM functions as an epigenetic regulator in the treatment of cancer[36].

Recent studies have also found that IVM could promote the death of tumor cells by regulating the tumor microenvironment in breast cancer. Under the stimulation of a tumor microenvironment with a high level of adenosine triphosphate (ATP) outside tumor cells, IVM could enhance the P2 × 4 / P2 × 7/Pannexin-1 mediated release of high mobility group box-1 protein (HMGB1) [37]. However, the release of a large amount of HMGB1 into the extracellular environment will promote immune cell-mediated immunogenic death and inflammatory reactions, which will have an inhibitory effect on the growth of tumor cells. Therefore, we believe that the anticancer effect of IVM is not limited to cytotoxicity, but also involves the regulation of the tumor microenvironment. IVM regulates the tumor microenvironment and mediates immunogenic cell death, which may be a new direction for research exploring anticancer mechanisms in the future.

2.2. Digestive system cancer

Gastric cancer is one of the most common malignant tumors worldwide. In the past year, more than one million patients with gastric cancer have been diagnosed worldwide [38]. Nambara's

study showed that IVM could significantly inhibit the proliferation of gastric cancer cells *in vivo* and *in vitro* and that the inhibitory effect of IVM depended on the expression of Yes-associated protein 1(YAP1)[39]. The gastric cancer cell lines MKN1 and SH-10-TC have higher YAP1 expression than MKN7 and MKN28 cells, so MKN1 and SH-10-TC cells are sensitive to IVM, while MKN7 and MKN28 are not sensitive to IVM.YAP1 plays an oncogenic role in tumorigenesis, indicating the possibility of the use of IVM as a YAP1 inhibitor for cancer treatment [40].

In a study that screened Wnt pathway inhibitors, IVM inhibited the proliferation of multiple cancers, including the colorectal cancer cell lines CC14, CC36, DLD1, and Ls174 T, and promoted apoptosis by blocking the Wnt pathway [41]. After intervention with IVM, the expression of caspase-3 in DLD1 and Ls174 T cells increased, indicating that IVM has an apoptosis-inducing effect and inhibits the expression of the downstream genes AXIN2, LGR5, and ASCL2 in the Wnt/β-catenin pathway. However, the exact molecular target of IVM that affects the Wnt/β-catenin pathway remains to be explored.

Hepatocellular carcinoma is the fourth leading cause of cancer death worldwide. Approximately 80% of cases of liver cancer are caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) infection [42]. IVM could inhibit the development of hepatocellular carcinoma by blocking YAP1 activity in spontaneous liver cancer *Mob1b*^{-/-} mice [43].Cholangiocarcinoma is a malignant tumor that originates in the bile duct inside and outside the liver. Intuyod's experiment found that IVM inhibited the proliferation of KKU214 cholangiocarcinoma cells in a dose- and time-dependent manner [44]. IVM halted the cell cycle in S phase and promoted apoptosis. Surprisingly, gemcitabine-resistant KKU214 cells showed high sensitivity to IVM, which suggested that IVM shows potential for the treatment of tumors that are resistant to conventional chemotherapy drugs.

2.3. Urinary system cancer

Renal cell carcinoma is a fatal malignant tumor of the urinary system derived from renal tubular epithelial cells. Its morbidity has increased by an average of 2% annually worldwide and the clinical treatment effect is not satisfactory [[45], [46], [47]]. Experiments confirmed that IVM could significantly inhibit the proliferation of five renal cell carcinoma cell lines without affecting the proliferation of normal kidney cells, and its mechanism may be related to the induction of mitochondrial dysfunction [48]. IVM could significantly reduce the mitochondrial membrane potential and inhibit mitochondrial respiration and ATP production. The presence of the mitochondrial fuel acetyl-L-carnitine (ALCAR), and the antioxidant N-acetyl-L-cysteine (NAC), could reverse IVM-induced inhibition. In animal experiments, the immunohistochemical results for IVM-treated tumor tissues showed that the expression of the mitochondrial stress marker HEL was significantly increased, and the results were consistent with those of the cell experiments.

Prostate cancer is a malignant tumor derived from prostate epithelial cells, and its morbidity is second only to that of lung cancer among men in Western countries [49]. In Nappi's experiment, it was found that IVM could enhance the drug activity of the anti-androgen drug enzalutamide in the prostate cancer cell line LNCaP and reverse the resistance of the prostate cancer cell line PC3

to docetaxel [50]. Interestingly, IVM also restored the sensitivity of the triple-negative breast cancer to the anti-estrogen drug tamoxifen [36], which also implies the potential for IVM to be used in endocrine therapy. Moreover, IVM was also found to have a good inhibitory effect on the prostate cancer cell line DU145 [51].

2.4. Hematological cancer

Leukemia is a type of malignant clonal disease caused by abnormal hematopoietic stem cells [52]. In an experiment designed to screen potential drugs for the treatment of leukemia, IVM preferentially killed leukemia cells at low concentrations without affecting normal hematopoietic cells [51]. The mechanism was related to the increase in the influx of chloride ions into the cell by IVM, resulting in hyperpolarization of the plasma membrane and induction of reactive oxygen species (ROS) production. It was also proven that IVM has a synergistic effect with cytarabine and daunorubicin on the treatment of leukemia. Wang's experiment found that IVM could selectively induce mitochondrial dysfunction and oxidative stress, causing chronic myeloid leukemia K562 cells to undergo increased caspase-dependent apoptosis compared with normal bone marrow cells [53]. It was also confirmed that IVM inhibited tumor growth in a dose-dependent manner, and dasatinib had improved efficacy.

2.5. Reproductive system cancer

Cervical cancer is one of the most common gynecological malignancies, resulting in approximately 530,000 new cases and 270,000 deaths worldwide each year. The majority of cervical cancers are caused by human papillomavirus (HPV) infection [54,55]. IVM has been proven to significantly inhibit the proliferation and migration of HeLa cells and promote apoptosis [56]. After intervention with IVM, the cell cycle of HeLa cells was blocked at the G1/S phase, and the cells showed typical morphological changes related to apoptosis.

Ovarian cancer is a malignant cancer that lacks early clinical symptoms and has a poor therapeutic response. The 5-year survival rate after diagnosis is approximately 47% [27,57]. In a study by Hashimoto, it found that IVM inhibited the proliferation of various ovarian cancer cell lines, and the mechanism was related to the inhibition of PAK1 kinase [58]. In research to screen potential targets for the treatment of ovarian cancer through the use of an shRNA library and a CRISPR/Cas9 library, the oncogene KPNB1 was detected. IVM could block the cell cycle and induce cell apoptosis through a KPNB1-dependent mechanism in ovarian cancer [59]. Interestingly, IVM and paclitaxel have a synergistic effect on ovarian cancer, and combined treatment in *in vivo* experiments almost completely inhibited tumor growth. Furthermore, according to a report by Zhang, IVM can enhance the efficacy of cisplatin to improve the treatment of epithelial ovarian cancer, and the mechanism is related to the inhibition of the Akt/mTOR pathway [60].

2.6. Brain glioma

Glioma is the most common cerebral tumor and approximately 100,000 people worldwide are diagnosed with glioma every year. Glioblastoma is the deadliest glioma, with a median survival time of only 14-17 months [61,62]. Experiments showed that IVM inhibited the proliferation of human glioblastoma U87 and T98 G cells in a dose-dependent manner and induced apoptosis in a caspase-dependent manner [63]. This was related to the induction of mitochondrial dysfunction and oxidative stress. Moreover, IVM could induce apoptosis of human brain microvascular endothelial cells and significantly inhibit angiogenesis. These results showed that IVM had the potential to resist tumor angiogenesis and tumor metastasis. In another study, IVM inhibited the proliferation of U251 and C6 glioma cells by inhibiting the Akt/mTOR pathway [64].

In gliomas, miR-21 can regulate the Ras/MAPK signaling pathway and enhance its effects on proliferation and invasion [65]. The DDX23 helicase activity affects the expression of miR-12 [66]. IVM could inhibit the DDX23/miR-12 signaling pathway by affecting the activity of DDX23 helicase, thereby inhibiting malignant biological behaviors. This indicated that IVM may be a potential RNA helicase inhibitor and a new agent for of tumor treatment. However, here, we must emphasize that because IVM cannot effectively pass the blood-brain barrier [67], the prospect of the use of IVM in the treatment of gliomas is not optimistic.

2.7. Respiratory system cancer

Nasopharyngeal carcinoma is a malignant tumor derived from epithelial cells of the nasopharyngeal mucosa. The incidence is obviously regional and familial, and Epstein-Barr virus (EBV) infection is closely related [68]. In a study that screened drugs for the treatment of nasopharyngeal cancer, IVM significantly inhibited the development of nasopharyngeal carcinoma in nude mice at doses that were not toxic to normal thymocytes [69]. In addition, IVM also had a cytotoxic effect on a variety of nasopharyngeal cancer cells in vitro, and the mechanism is related to the reduction of PAK1 kinase activity to inhibit the MAPK pathway.

Lung cancer has the highest morbidity and mortality among cancers [70]. Nishio found that IVM could significantly inhibit the proliferation of H1299 lung cancer cells by inhibiting YAP1 activity [43]. Nappi's experiment also proved that IVM combined with erlotinib to achieved a synergistic killing effect by regulating EGFR activity and in HCC827 lung cancer cells [50]. In addition, IVM could reduce the metastasis of lung cancer cells by inhibiting EMT.

2.8. Melanoma

Melanoma is the most common malignant skin tumor with a high mortality rate. Drugs targeting BRAF mutations such as vemurafenib, dabrafenib and PD-1 monoclonal antibodies, including pembrolizumab and nivolumab have greatly improved the prognosis of melanoma [71,72]. Gallardo treated melanoma cells with IVM and found that it could effectively inhibit melanoma activity [73]. Interestingly, IVM could also show activity against BRAF wild-type melanoma cells, and its combination with dabrafenib could significantly increase antitumor activity. Additionally, it has been confirmed that PAK1 is the key target of IVM that mediates its anti-melanoma activity, and IVM can also significantly reduce the lung metastasis of melanoma in animal experi-

ments. Deng found that IVM could activate the nuclear translocation of TFE3 and induce autophagy-dependent cell death by dephosphorylation of TFE3 (Ser321) in SK-MEL-28 melanoma cells [74]. However, NAC reversed the effect of IVM, which indicated that IVM increased TFE3-dependent autophagy through the ROS signaling pathway.

3. IVM-induced programmed cell death in tumor cells and related mechanisms

3.1. Apoptosis

IVM induces different programmed cell death patterns in different tumor cells (Table 1). As shown in Table 1, the main form of IVM induced programmed cell death is apoptosis. Apoptosis is a programmed cell death that is regulated by genes to maintain cell stability. It can be triggered by two activation pathways: the endogenous endoplasmic reticulum stress/mitochondrial pathway and the exogenous death receptor pathway [75,76]. The decrease in the mitochondrial membrane potential and the cytochrome c is released from mitochondria into the cytoplasm was detected after the intervention of IVM in Hela cells [56]. Therefore, we infer that IVM induces apoptosis mainly through the mitochondrial pathway. In addition, morphological changes caused by apoptosis, including chromatin condensation, nuclear fragmentation, DNA fragmentation and apoptotic body formation were observed. Finally, IVM changed the balance between apoptosis-related proteins by upregulating the protein Bax and downregulating anti-apoptotic protein Bcl-2, thereby activating caspase-9/-3 to induce apoptosis [48,53,63] (Fig. 2).

Table 1

Summary of IVM promotes programmed cell death.

programmed cell death	Tumor cell line	References
Apoptosis	Colorectal cancer (CC14, CC36, DLD1, LS174T) Ovarian cancer (SKOV3, OVCAR3, CAOV3) Renal cell carcinoma (SW-839, Caki-2, 786-0, A498, ACHN) Leukemia (K562, primary CD34 ⁺ CML cell) Glioblastoma (U87, T98 G)	[56][41][59][48][53][63]
Autophagy	Glioma (U251, C6) Breast cancer (MCF-7, MDA-MB-231) Melanoma (SK-MEL-28)	[64][32][74]
Pyroptosis	Breast cancer (MDA-MB-231, 4T1)	[37]

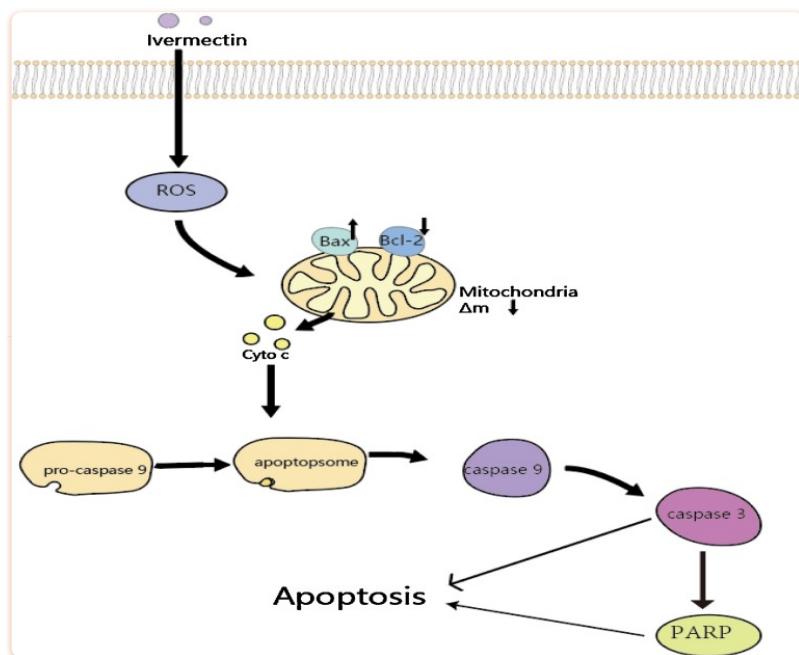


Fig. 2

Mechanisms of IVM-induced mitochondria-mediated apoptosis.

Cancer cells exposure to IVM can be induced to generate ROS generation and reduce membrane potential of mitochondria. Moreover, IVM can up-regulate Bax and down-regulate Bcl-2, promote releasing of cytochrome C into the cytosol, and activate the signaling cascade of caspases-9/3. Finally, activated PARP and caspase-3 trigger apoptosis.

3.2. Autophagy

Autophagy is a lysosomal-dependent form of programmed cell death. It utilizes lysosomes to eliminate superfluous or damaged organelles in the cytoplasm to maintain homeostasis. It is characterized by double-layered or multilayered vacuolar structures containing cytoplasmic components, which are known as autophagosomes [77]. In recent years, many studies have shown that autophagy is a double-edged sword in tumor development. On the one hand, autophagy can help tumors adapt to the nutritional deficiency of the tumor microenvironment, and to a certain extent, protect tumor cells from chemotherapy- or radiotherapy- induced injury. On the other hand, some autophagy activators can increase the sensitivity of tumors to radiotherapy and chemotherapy by inducing autophagy, and excessive activation of autophagy can also lead to tumor cell death [[78], [79], [80], [81]]. Overall, the specific environment of tumor cells will determine whether autophagy enhances or inhibits tumor development and improving autophagy activity has also become a new approach in cancer therapy. Programmed cell death mediated by autophagy after IVM intervention and the enhancement of the anticancer efficacy of IVM by regulating autophagy are interesting topics. Intervention with IVM in the breast cancer cell lines MCF-7 and MDA-MB-231 significantly increased intracellular autophagic flux and the expression

of key autophagy proteins such as LC3, Bclin1, Atg5, and the formation of autophagosomes can be observed [32]. However, after using the autophagy inhibitors chloroquine and wortmannin or knocking down Bclin1 and Atg5 by siRNA to inhibit autophagy, the anticancer activity of IVM significantly decreased. This proves that IVM mainly exerts an antitumor effect through the autophagy pathway. In addition, researchers also used the Akt activator CA-Akt to prove that IVM mainly induces autophagy by inhibiting the phosphorylation of Akt and mTOR (Fig. 3). The phenomenon of IVM-induced autophagy has also been reported in glioma and melanoma [64,74]. All of the above findings indicate the potential of IVM as an autophagy activator to induce autophagy-dependent death in tumor cells.

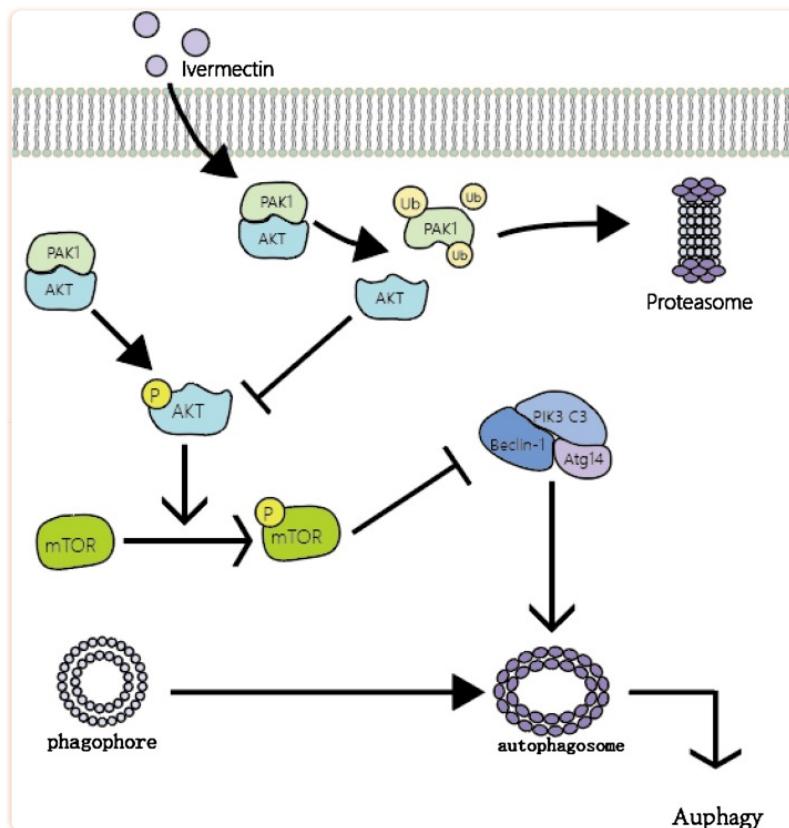


Fig.3

Mechanisms of IVM-induced PAK1/Akt/mTOR-mediated autophagy.

IVM promotes degradation of PAK1 by ubiquitination/proteasome pathway, thereby inhibiting the Akt/mTOR signaling pathway. Subsequently, the inactivation Akt/mTOR signaling cannot inhibit the formation of the Beclin-1 complex, thus inducing the formation autophagosome. Overall, IVM can induce autophagy through PAK1/Akt/mTOR pathway to represses the growth of cancer cells independent of apoptosis.

(Ub:Ubiquitination, P:Phosphorylation)

3.3. Cross talk between IVM-induced apoptosis and autophagy

The relationship between apoptosis and autophagy is very complicated, and the cross talk between the two plays a vital role in the development of cancer [82]. Obviously, the existing results suggest that IVM-induced apoptosis and autophagy also exhibit cross talk. For example, it was found in SK-MEL-28 melanoma cells that IVM can promote apoptosis as well as autophagy [74]. After using the autophagy inhibitor baflomycin A1 or siRNA to downregulate Beclin1, IVM-induced apoptosis was significantly enhanced, which suggested that enhanced autophagy will reduce IVM-induced apoptosis and that IVM-induced autophagy can protect tumor cells from apoptosis. However, in breast cancer cell experiments, it was also found that IVM could induce autophagy, and enhanced autophagy could increase the anticancer activity of IVM [37]. The latest research shows that in normal circumstances autophagy will prevent the induction of apoptosis and apoptosis-related caspase enzyme activation will inhibit autophagy. However, in special circumstances, autophagy may also help to induce apoptosis or necrosis [83]. In short, the relationship between IVM-induced apoptosis and autophagy involves a complex regulatory mechanism, and the specific molecular mechanism needs further study. We believe that deeper exploration of the mechanism can further guide the use of IVM in the treatment of cancer.

3.4. Pyroptosis

Pyroptosis is a type of inflammatory cell death induced by inflammasomes. The inflammasome is a multimolecular complex containing pattern recognition receptor (PRR), apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase-1. PRR can identify pathogen-associated molecular patterns (PAMPs) that are structurally stable and evolutionarily conserved on the surface of pathogenic microorganisms and damage-associated molecular patterns (DAMPs) produced by damaged cells [84,85]. Inflammasomes initiate the conversion of pro-caspase-1 via self-shearing into activated caspase-1. Activated caspase-1 can cause pro-IL-1 β and pro-IL-18 to mature and to be secreted. Gasdermin D(GSDMD) is a substrate for activated caspase-1 and is considered to be a key protein in the execution of pyroptosis [86,87]. In an experiment by Draganov, it was found that the release of lactate dehydrogenase (LDH) and activated caspase-1 was significantly increased in breast cancer cells after IVM intervention [37]. In addition, characteristic pyroptosis phenomena such as cell swelling and rupturing were observed. The authors speculated that IVM may mediate the occurrence of pyroptosis via the P2 \times 4/P2 \times 7/NLRP3 pathway (Fig. 4), but there is no specific evidence to prove this speculation. Interestingly, in ischemia-reperfusion experiments, IVM aggravated renal ischemia via the P2 \times 7/NLRP3 pathway and increased the release of proinflammatory cytokines in human proximal tubular cells [88]. Although there is currently little evidences showing that IVM induces pyroptosis, it is important to investigate the role of IVM in inducing pyroptosis in other cancers in future studies and realize that IVM may induce different types of programmed cell death in different types of cancer.

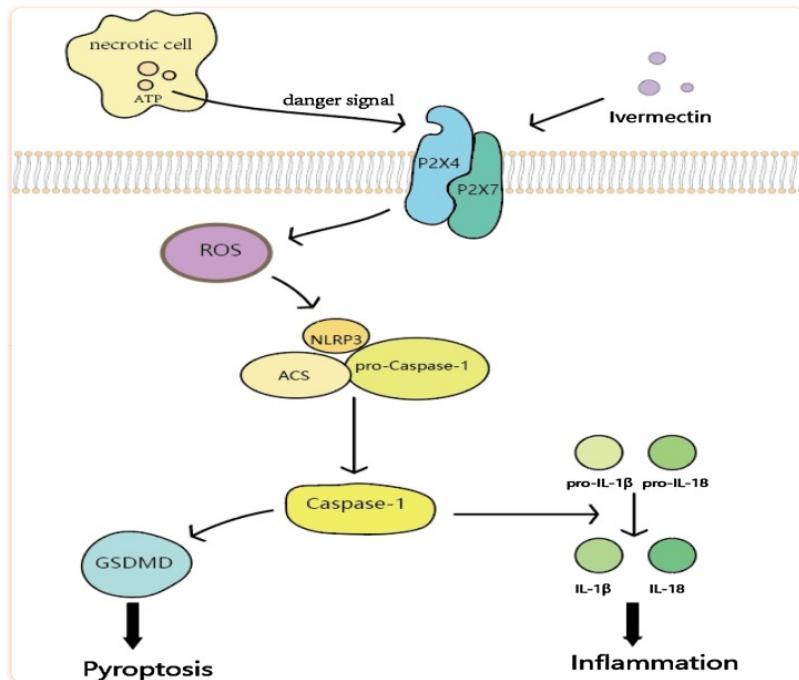


Fig. 4

Mechanisms of IVM-induced P2x4/P2x7/NLRP3-mediated pyroptosis.

IVM can promote ROS release in cancer cells by P2x4/P2x7 receptors. Cellular ROS can activate NLRP3 Inflammasome including ASC, NLRP3 and pro-caspase-1 assemble. Subsequently, NLRP3 Inflammasome initiates pro-caspase-1 to self-shear into mature caspase-1. On the one hand, activated caspase-1 induces the secretion of pro-inflammatory cytokines IL-1 β and IL-18. On the other hand, caspase-1 activated by GSDMD triggers pyroptosis independent of apoptosis.

4. Anticancer effect of IVM through other pathways

4.1. Cancer stem cells

Cancer stem cells (CSCs) are a cell population similar to stem cells with characteristics of self-renewal and differentiation potential in tumor tissue [89,90]. Although CSCs are similar to stem cells in terms of function, because of the lack of a negative feedback regulation mechanism for stem cell self-renewal, their powerful proliferation and multidirectional differentiation abilities are unrestricted, which allows CSCs to maintain certain activities during chemotherapy and radiotherapy [90, 91, 92]. When the external environment is suitable, CSCs will rapidly proliferate to reactivate the formation and growth of tumors. Therefore, CSCs have been widely recognized as the main cause of recurrence after treatment [93,94]. Guadalupe evaluated the effect of IVM on CSCs in the breast cancer cell line MDA-MB-231 [95]. The experimental results showed that IVM would preferentially targeted and inhibited CSCs-rich cell populations compared with other cell populations in MDA-MB-231 cells. Moreover, the expression of the homeobox protein

NANOG, octamer-binding protein 4 (OCT-4) and SRY-box 2 (SOX-2), which are closely related to the self-renewal and differentiation ability of stem cells in CSCs, were also significantly inhibited by IVM. This suggests that IVM may be used as a potential CSCs inhibitor for cancer therapy. Further studies showed that IVM could inhibit CSCs by regulating the PAK1-STAT3 axis [96].

4.2. Reversal of tumor multidrug resistance

MDR of tumor cells is the main cause of relapses and deaths after chemotherapy [97]. ATP binding transport family-mediated drug efflux and overexpression of P-glycoprotein (P-gp) are widely considered to be the main causes of tumor MDR [98], [99], [100]. Several studies have confirmed that IVM could reverse drug resistance by inhibiting P-gp and MDR-associated proteins [101], [102], [103]. In Didier's experiments testing the effect of IVM on lymphocytic leukemia, IVM could be used as an inhibitor of P-gp to affect MDR [22]. In Jiang's experiment, IVM reversed the drug resistance of the vincristine-resistant colorectal cancer cell line HCT-8, doxorubicin-resistant breast cancer cell line MCF-7 and the chronic myelogenous leukemia cell line K562 [104]. IVM inhibited the activation of EGFR and the downstream ERK/Akt/NF-kappa B signaling pathway to downregulate the expression of P-gp. Earlier, we mentioned the role of IVM in docetaxel-resistant prostate cancer [50] and gemcitabine-resistant cholangiocarcinoma [44]. These results indicated the significance of applying IVM for the treatment of chemotherapy patients with MDR.

4.3. Enhanced targeted therapy and combined treatment

Targeted treatment of key mutated genes in cancer, such as EGFR in lung cancer and HER2 in breast cancer, can achieve powerful clinical effects [105,106]. HSP27 is a molecular chaperone protein that is highly expressed in many cancers and associated with drug resistance and poor prognosis. It is considered as a new target for cancer therapy [107]. Recent studies have found that IVM could be used as an inhibitor of HSP27 phosphorylation to enhance the activity of anti-EGFR drugs in EGFR/HER2- driven tumors. An experiment found that IVM could significantly enhance the inhibitory effects of erlotinib and cetuximab on lung cancer and colorectal cancer [50]. Earlier, we mentioned that IVM combined with conventional chemotherapeutic drugs such as cisplatin [60], paclitaxel [59], daunorubicin and cytarabine [51], or with targeted drugs such as dasatinib [53] and dapafenib [73] shows great potential for cancer treatment. The combination of drugs can effectively increase efficacy, reduce toxicity or delay drug resistance. Therefore, combination therapy is the most common method of chemotherapy. IVM has a variety of different mechanisms of action in different cancers, and its potential for synergistic effects and enhanced efficacy in combination therapy was of particular interest to us. Not only does IVM not overlap with other therapies in term of its mechanism of action, but the fact that of IVM has multiple targets suggests that it is not easy to produce IVM resistance. Therefore, continued study and testing of safe and effective combination drug therapies is essential to maximize the anti-cancer effects of IVM.

5. Molecular targets and signaling pathways involved in the anticancer potential of

IVM

As mentioned above, the anticancer mechanism of IVM involves a wide range of signaling pathways such as Wnt/β-catenin, Akt/mTOR, MAPK and other possible targets such as PAK1 and HSP27, as well as other mechanisms of action ([Table 2](#)). We found that IVM inhibits tumor cell development in a PAK1-dependent manner in most cancers. Consequently, we have concentrated on discussing the role of PAK1 kinase and cross-talk between various pathways and PAK1 to provide new perspectives on the mechanism of IVM function.

Table 2

Summary of the anticancer mechanism of IVM

Mechanism	Cancer type	References
Inhibit Wnt pathway	Breast cancer, Colorectal cancer	[33,41]
Inhibit Akt/mTOR pathway	Breast cancer, Ovarian cancer, Glioma	[32,60,64]
Inhibit MAPK pathway	Nasopharyngeal carcinoma Melanoma	[69,73]
Inhibit YAP1 protein	Gastric cancer, liver cancer	[39,43]
Inhibit PAK1 protein	Breast cancer, Ovarian cancer, Nasopharyngeal carcinoma, Melanoma	[32,58,69,73,96]
Inhibit HSP27	Prostate cancer, Lung cancer Colorectal cancer	[50]
Induce mitochondrial dysfunction	Renal cell carcinoma, Glioma Leukemia	[48,53,63]
Inhibit cancer stem cells	Breast cancer	[95,96]
Inhibit p-glycoprotein and MDR protein	Colorectal cancer, Breast cancer Leukemia	[22,104]
Activate P2 × 7 receptor	Breast cancer	[37]
Inhibit SIN3 domain	Breast cancer	[36]
Inhibit DDX23 helicase	Glioma	[66]
Activate chloride channels	Leukemia	[51]
Increase TFE3 Activity	Melanoma	[74]
Inhibit KPNB1 protein	Ovarian cancer	[59]

As a member of the PAK family of serine/threonine kinases, PAK1 has a multitude of biological functions such as regulating cell proliferation and apoptosis, cell movement, cytoskeletal dynamics and transformation [[108](#)]. Previous studies have indicated that PAK1 is located at the intersection of multiple signaling pathways related to tumorigenesis and is a key regulator of cancer

signaling networks (Fig. 5). The excessive activation of PAK1 is involved in the formation, development, and invasion of various cancers [109,110]. Targeting PAK1 is a novel and promising method for cancer treatment, and the development of PAK1 inhibitors has attracted widespread attention [111]. IVM is a PAK1 inhibitor in a variety of tumors, and it has good safety compared to that of other PAK1 inhibitors such as IPA-3. In melanoma and nasopharyngeal carcinoma, IVM inhibited cell proliferation activity by inhibiting PAK1 to downregulate the expression of MEK 1/2 and ERK1/2 [69,73]. After IVM intervention in breast cancer, the expression of PAK1 was also significantly inhibited, and the use of siRNA to downregulate the expression of PAK1 in tumor cells significantly reduced the anticancer activity of IVM. Interestingly, IVM could inhibit the expression of PAK1 protein but did not affect the expression of PAK1 mRNA [32]. The proteasome inhibitor MG132 reversed the suppressive effect of IVM, which indicated that IVM mainly degraded PAK1 via the proteasome ubiquitination pathway. We have already mentioned that IVM plays an anticancer role in various tumors by regulating pathways closely related to cancer development. PAK1 is at the junction of these pathways. Overall, we speculate that IVM can regulate the Akt/mTOR, MAPK and other pathways that are essential for tumor cell proliferation by inhibiting PAK1 expression, which plays an anticancer role in most cancers.

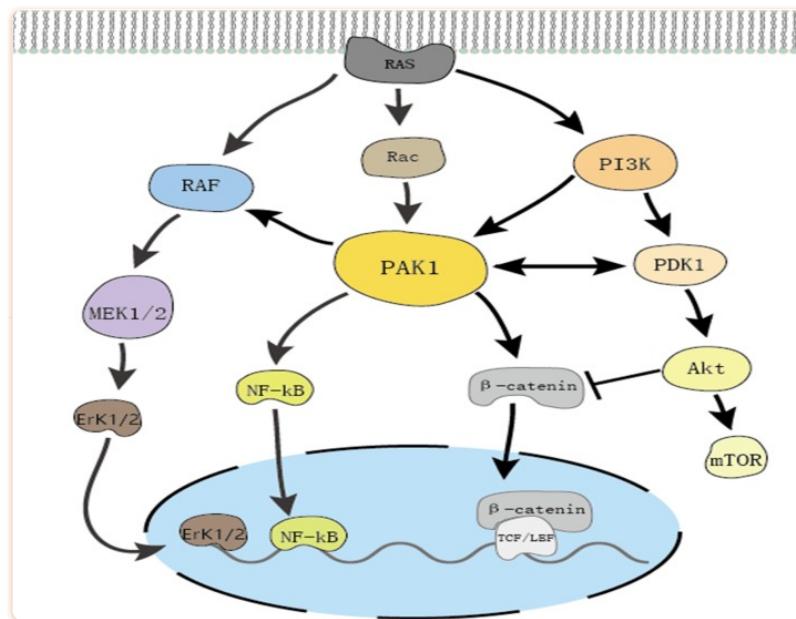


Fig. 5

PAK1 cross regulate multiple signal pathways.

RAS activation directly initiates PAK1, MAPK and PI3K/Akt pathway. PAK1 allocates crosstalk between the PI3K and MAPK pathways. PAK1 can induce MEK1/2 and ERK1/2 activation by RAF and increase PI3K/Akt signaling by PDK1. PAK1 can also activate pro-inflammatory pathways by facilitating nuclear activation of NF- κ B. In addition, PAK1 facilitates Wnt/ β -catenin signaling, make β -catenin accumulate in the cytoplasm and translocate to the nucleus. Moreover, Akt can inhibit β -catenin transfer into nucleus.

6. Summary and outlooks

Malignant tumors are one of the most serious diseases that threaten human health and social development today, and chemotherapy is one of the most important methods for the treatment of malignant tumors. In recent years, many new chemotherapeutic drugs have entered the clinic, but tumor cells are prone to drug resistance and obvious adverse reactions to these drugs. Therefore, the development of new drugs that can overcome resistance, improve anticancer activity, and reduce side effects is an urgent problem to be solved in chemotherapy. Drug repositioning is a shortcut to accelerate the development of anticancer drugs.

As mentioned above, the broad-spectrum antiparasitic drug IVM, which is widely used in the field of parasitic control, has many advantages that suggest that it is worth developing as a potential new anticancer drug. IVM selectively inhibits the proliferation of tumors at a dose that is not toxic to normal cells and can reverse the MDR of tumors. Importantly, IVM is an established drug used for the treatment of parasitic diseases such as river blindness and elephantiasis. It has been widely used in humans for many years, and its various pharmacological properties, including long- and short-term toxicological effects and drug metabolism characteristics are very clear. In healthy volunteers, the dose was increased to 2 mg/Kg, and no serious adverse reactions were found, while tests in animals such as mice, rats, and rabbits found that the median lethal dose (LD50) of IVM was 10-50 mg/Kg [112]. In addition, IVM has also been proven to show good permeability in tumor tissues [50]. Unfortunately, there have been no reports of clinical trials of IVM as an anticancer drug. There are still some problems that need to be studied and resolved before IVM is used in the clinic.

(1) Although a large number of research results indicate that IVM affects multiple signaling pathways in tumor cells and inhibits proliferation, IVM may cause antitumor activity in tumor cells through specific targets. However, to date, no exact target for IVM action has been found. (2) IVM regulates the tumor microenvironment, inhibits the activity of tumor stem cells and reduces tumor angiogenesis and tumor metastasis. However, there is no systematic and clear conclusion regarding the related molecular mechanism. Therefore, in future research, it is necessary to continue to explore the specific mechanism of IVM involved in regulating the tumor microenvironment, angiogenesis and EMT. (3) It has become increasingly clear that IVM can induce a mixed cell death mode involving apoptosis, autophagy and pyroptosis depending on the cell conditions and cancer type. Identifying the predominant or most important contributor to cell death in each cancer type and environment will be crucial in determining the effectiveness of IVM-based treatments. (4) IVM can enhance the sensitivity of chemotherapeutic drugs and reduce the production of resistance. Therefore, IVM should be used in combination with other drugs to achieve the best effect, while the specific medication plan used to combine IVM with other drugs remains to be explored.

Most of the anticancer research performed on the avermectin family has been focused on avermectin and IVM until now. Avermectin family drugs such as selamectin [36,41,113], and doramectin [114] also have anticancer effects, as previously reported. With the development of derivatives of the avermectin family that are more efficient and less toxic, relevant research on the

anticancer mechanism of the derivatives still has great value. Existing research is sufficient to demonstrate the great potential of IVM and its prospects as a novel promising anticancer drug after additional research. We believe that IVM can be further developed and introduced clinically as part of new cancer treatments in the near future.

Declaration of Competing Interest

The authors report no declarations of interest.

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